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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,321	10/26/2001	Liming Shao	SPV-045.01	1490

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,321	SHAO, LIMING	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 8-25-05 is acknowledged.

Claims included in the prosecution are 26-28 and 30.

Claim Rejections - 35 USC ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 26-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/47203 of record.

WO teaches formulations containing narcotic analgesics such as fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin for oral administration. According to WO, this cyclodextrin is an oral absorption enhancer (abstract, page 7, lines 10-11, examples and claims). Although WO does not teach all the fentanyl based compounds and do not provide examples of fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin for oral administration, it would have been obvious to one of ordinary skill in the art to use any fentanyl based compound in combination with hydroxypropyl-beta cyclodextrin, with a reasonable expectation of success since it is a absorption enhancer.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Example 6 in the reference is the only example comprising fentanyl citrate and this example does not specify the identity of the absorption enhancer. Applicant further argues that the example does not provide control data to determine if the absorption enhancer in question is actually enhancing absorption. This argument is not found to be persuasive since if the reference had identified the enhancer as a cyclodextrin, then it would have been a 102 reference. The reference is suggestive of the use of cyclodextrin since it is an absorption enhancer and therefore, one of ordinary skill in the art would be motivated to use the enhancer suggested by the reference. Applicant further argues that example 6 does not provide control data to determine if the absorption enhancer is actually enhancing absorption. Applicant further argues that the data only indicates that some effect on rats 636 and 637 was observed when the formulation was administered via pipette and no effect at all was observed on rats with numbers 632, 633 and 634. These arguments are not found to be persuasive since instant claims do not define what the mode of oral administration is. With regard to applicant's arguments that this example shows only some effect, the examiner points out that patent office is not equipped to determine whether the effect observed in the reference is sufficient or not sufficient and applicant has not shown by comparative studies that the effect observed by instant method is more than that observed in the reference. Furthermore, a careful evaluation of the results obtained in Example 1 of instant specification indicates 1) that only average values of two animals per group; 2) no statistical evaluation has been performed and 3)

no differences were seen at 15 minute interval between 10 % gamma-HPCD and saline control. Furthermore, while the claims are drawn to multitudes of compounds, the experiment was performed only on Fentanyl. On the same basis, applicant's arguments regarding 'long-felt need' are not persuasive.

Upon consideration, the rejection of claims over WO 92/02256 cited above, further in view of Farrar et al (JNCI, 1998), Portenoy et al (Pain, 1999), Stanley et al (Anesth. Analg. 1989) by themselves is withdrawn.

3. Claims 26-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farrar et al (JNCI, 1998), or Portenoy et al (Pain, 1999), or Stanley et al (Anesth. Analg. 1989) (all are of record) in combination with Chiesi (4,603,123), Bodor (5,231,089), Dwivedi 6,740,639) and WO 92/02256.

As pointed out before, The references of Farrar et al, Porenoy et al, Stanley et al and WO each teach the efficacy of fentanyl in treating pain when administered orally (note abstracts in each). What is lacking in these references is teaching of the carrier, cyclodextrin.

Chiesi while disclosing formulations containing the analgesic drug, piroxicam teaches that piroxicam is highly insoluble in water and complexation with cyclodextrins solubilizes them and such a complex is rapidly absorbed and better tolerated when administered orally (abstract, col. 1, lines 23-37, col. 3, line 48 et seq., columns 7-8).

Bodor while disclosing formulations containing carbamazepine teaches that formulating this compound into inclusion complexes of cyclodextrins enables the oral

dosage forms capable of achieving therapeutic blood levels rapidly and that the inclusion complex can be administered at much lower dosage levels (abstract, col. 7, lines 38-53, col. 14, lines 12-36 and claim 1).

Dwivedi teaches that complexation with cyclodextrins increases the solubility of an opioid peptide. According to Dwivedi, the complexes have better solubility, improved biopharmaceutical properties such as lesser toxicity, better analgesic and non-addition properties (abstract).

As pointed out in the previous action, WO 92 teaches the knowledge in the art of the formation of complexes between cyclodextrins and fentanyl (note the abstract, Examples and claim 16).

It would have been obvious to one of ordinary skill in the art to use cyclodextrins as carriers for the oral administration of fentanyl taught by Farrer, Portenoy or Stanley since the references of Chiesi, Bodor, and Dwivedi show that inclusion complexes of cyclodextrins increase the solubility of water insoluble drugs, increase their bioavailability, lesser toxicity and better therapeutic properties. One skilled in the art would be motivated to use cyclodextrin inclusion complexes orally since WO 92 shows the knowledge in the art of preparing the inclusion of complexes of Fentanyl.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that it is improper to combine references where the references teach away from their combination. According to applicant it is improper to combine Chiesi, Bodor, Dwivedi and WO 92 with Farrer or Portenoy or Stanley. Applicant argues that that there is no suggestion or motivation to modify WO 92 for oral

administration. According to applicant, the stated intended purpose of the invention in WO 92 is to limit distribution of the drug to the neuraxis of a patient, i.e., the drug is prevented from dispersing throughout the body, such as by migration via the circulatory system. Further according to applicant, the disclosures of Farrar, Portenoy and Stanley teach oral administration of fentanyl citrate which leads to widespread distribution of the drug throughout the body and likewise, the disclosures of Chiesi, Bodor and Dwivedi teach oral administration of cyclodextrin complexes which leads to widespread distribution of the complexed drugs throughout the body, contrary to the teachings of WO 92. These arguments are not persuasive. First of all, the examiner agrees with applicant that it is improper to combine the references when the references teach away from their combination. However, that is not the case with instant combination since WO 92 is combined for its teachings of the knowledge in the art of the encapsulation of fentanyl in cyclodextrin and not for its teachings of the mode of administration. The primary references clearly teach the effectiveness of orally administered fentanyl. These references lack only the teachings of cyclodextrin as the carrier for fentanyl. The secondary references of Chiesi, Bodor and Dwivedi clearly show the advantages of using cyclodextrins as carriers for various drugs and WO 92 is combined with these references since WO 92 teaches the knowledge in the art of the use of cyclodextrins as carriers for fentanyl itself. One of ordinary skill in the art thus, would be motivated to administer fentanyl by oral administration and using art known carrier for fentanyl, i.e., cyclodextrins because of the advantages of cyclodextrins as carriers in oral

administration itself, as taught by the secondary references. Therefore, applicant's arguments that the reference of WO 92 teaches away are not persuasive.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 26-28 and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-26 of U.S. Patent No. 6,635661. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in instant invention and the patented claims are drawn to a method of treatment of same conditions. Instant claims recite compounds which are species falling within the generic formula in the patented claims (when R6 and R5 are hydrogen in the group R6R5C-R4, linking the hetero Nitrogen atom in the ring structure). Furthermore, instant compositions recite in addition, cyclodextrin. Although patented claims do not recite cyclodextrin, the claims recite 'comprising' and that cyclodextrin could be a carrier is evident from the disclosure of the

said patent (see col. 45, line 33 and also claim 18 of the patent). The species of the compound and the carrier is anticipated by the claims in the said patent.

The rejection is maintained in the absence of the terminal disclaimer.

The reference of Kim (5,759,573) which teaches cyclodextrin liposomes containing fentanyl is cited of interest (abstract, col. 5, line 56 and claims).

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/G S Kishore/

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK